Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Cystic Fibrosis Foundation pulmonary guidelines. Use of cystic fibrosis transmembrane conductance regulator modulator therapy in patients with cystic fibrosis.

Bibliographic Source(s)

Ren CL, Morgan RL, Oermann C, Resnick HE, Brady C, Campbell A, DeNagel R, Guill M, Hoag J, Lipton A, Newton T, Peters S, Willey-Courand DB, Naureckas ET. Cystic Fibrosis Foundation pulmonary guidelines. Use of cystic fibrosis transmembrane conductance regulator modulator therapy in patients with cystic fibrosis. Ann Am Thorac Soc. 2018 Mar;15(3):271-80. [44 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

NEATS Assessment

National Guideline Clearinghouse (NGC) has assessed this guideline's adherence to standards of trustworthiness, derived from the Institute of Medicine's report Clinical Practice Guidelines We Can Trust.

= Poor = Fair = Good = Very Good = Excellent

Assessment	Standard of Trustworthiness
YES	Disclosure of Guideline Funding Source
	Disclosure and Management of Financial Conflict of Interests
	Guideline Development Group Composition
YES	Multidisciplinary Group

YES	Methodologist Involvement
▮▮▮▮▯	Patient and Public Perspectives
	Use of a Systematic Review of Evidence
▮▮▮▮▮	Search Strategy
▮▮▮▮▮	Study Selection
▮▮▮▮▮	Synthesis of Evidence
	Evidence Foundations for and Rating Strength of Recommendations
▮▮▮▯▯	Grading the Quality or Strength of Evidence
▮▮▮▮▮	Benefits and Harms of Recommendations
▮▮▮▮▮	Evidence Summary Supporting Recommendations
▮▮▮▮▮	Rating the Strength of Recommendations
▮▮▮▮▮	Specific and Unambiguous Articulation of Recommendations
▮▯▯▯▯	External Review
▮▮▯▯▯	Updating

Recommendations

Major Recommendations

Definitions of the strength of recommendations (Strong, Conditional) and quality of the evidence (High, Moderate, Low, Very Low) are provided at the end of the "Major Recommendations" field.

Note from the National Guideline Clearinghouse (NGC): See the original guideline document for remarks regarding the recommendations.

Question 1: Should Ivacaftor (IVA) versus No Cystic Fibrosis (CF) Transmembrane Conductance Regulator (CFTR) Modulator Treatment Be Used for Individuals with a CF Diagnosis due to Gating Mutations Other Than G551D or R117H (i.e., G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, or G1349D)?

Recommendation 1. The committee recommends IVA for individuals aged 2–5 years with a diagnosis of CF and gating mutations other than G551D or R117H. For individuals under 2 years of age, the committee makes no recommendation. See the National Guideline Clearinghouse (NGC) summary of the Cystic Fibrosis Foundation guideline Clinical practice guidelines from the Cystic Fibrosis Foundation for preschoolers with cystic fibrosis.

Recommendation 2. The committee suggests IVA for individuals aged 6–11 years with a diagnosis of CF with percent predicted forced expiratory volume in 1 second ($PPFEV_1$) less than 40% and a gating mutation other than G551D or R117H (Conditional recommendation; Very Low certainty in the evidence).

Recommendation 3. The committee suggests IVA treatment for individuals aged 6–11 years with a diagnosis of CF with $PPFEV_1$ 40%–90% and a gating mutation other than G551D or R117H (Conditional recommendation; Low certainty in the evidence).

Recommendation 4. The committee suggests IVA be used for individuals aged 6–11 years with a diagnosis of CF with $PPFEV_1$ greater than 90% and a gating mutation other than G551D or R117H (Conditional recommendation; Very Low certainty in the evidence).

Recommendation 5. The committee suggests IVA for individuals aged 12–17 years with a diagnosis of CF with $PPFEV_1$ less than 40% and a gating mutation other than G551D or R117H (Conditional recommendation; Low certainty in the evidence).

Recommendation 6. The committee suggests IVA for individuals aged 12–17 years with a diagnosis of CF with $PPFEV_1$ 40%– 90% and a gating mutation other than G551D or R117H (Conditional recommendation; Moderate certainty in the evidence).

Recommendation 7. The committee suggests IVA for individuals aged 12–17 years with a diagnosis of CF with $PPFEV_1$ greater than 90% and a gating mutation other than G551D or R117H (Conditional recommendation; Moderate certainty in the evidence).

Recommendation 8. The committee suggests IVA for individuals aged 18 years or older with a diagnosis of CF with $PPFEV_1$ less than 40% and a gating mutation other than G551D or R117H (Conditional recommendation; Low certainty in the evidence).

Recommendation 9. The committee suggests IVA for individuals with a diagnosis of CF aged 18 years or older with $PPFEV_1$ 40%–90% and a gating mutation G551D or R117H (Conditional recommendation; Moderate certainty in the evidence).

Recommendation 10. The committee suggests IVA for individuals aged 18 years or older with a diagnosis of CF with $PPFEV_1$ greater than 90% and a gating mutation G551D or R117H (Conditional recommendation; Moderate certainty in the evidence).

Question 2: Should IVA versus No CFTR Modulator Treatment Be Used for Individuals with a CF Diagnosis Due to the R117H Mutation?

Recommendation 11. The committee suggests against IVA therapy for individuals aged 0–5 years and with a CF diagnosis due to the R117H mutation (Conditional recommendation; Very Low certainty in the evidence).

Recommendation 12. The committee suggests IVA for individuals aged 6–11 years with $PPFEV_1$ less than 40% with a diagnosis of CF due to the R117H mutation (Conditional recommendation; Very Low certainty in the evidence).

Recommendation 13. The committee suggests IVA treatment for individuals aged 6–11 years with $PPFEV_1$ 40%–90% with a diagnosis of CF due to the R117H mutation (Conditional recommendation; Very Low certainty in the evidence).

Recommendation 14. The committee suggests that IVA not be used for individuals aged 6–11 years with $PPFEV_1$ greater than 90% with a diagnosis of CF due to the R117H mutation (Conditional recommendation; Low certainty in the evidence).

Recommendation 15. The committee suggests IVA for individuals aged 12–17 years with $PPFEV_1$ less than 40% with a diagnosis of CF due to the R117H mutation (Conditional recommendation; Very Low certainty in the evidence).

Recommendation 16. The committee suggests IVA for individuals aged 12–17 years with $PPFEV_1$ 40%–90% with a diagnosis of CF due to the R117H mutation (Conditional recommendation; Very Low certainty

in the evidence).

Recommendation 17. The committee suggests against IVA for individuals aged 12–17 years with $PPFEV_1$ greater than 90% with a diagnosis of CF due to the R117H mutation (Conditional recommendation; Moderate certainty in the evidence).

Recommendation 18. The committee suggests IVA for individuals aged 18 years or older with $PPFEV_1$ less than 40% with a diagnosis of CF due to the R117H mutation (Conditional recommendation; Very Low certainty in the evidence).

Recommendation 19. The committee suggests IVA for individuals aged 18 years or older with $PPFEV_1$ 40%–90% with a diagnosis of CF due to the R117H mutation (Conditional recommendation; Moderate certainty in the evidence).

Recommendation 20. The committee suggests IVA for individuals aged 18 years or older with $PPFEV_1$ greater than 90% with a diagnosis of CF due to the R117H mutation (Conditional recommendation; Moderate certainty in the evidence).

Question 3: Should IVA/Lumacaftor (LUM) Combination Drug versus No CFTR Modulator Treatment Be Used in Individuals with Two Copies of the F508del Mutation?

Recommendation 21. The committee makes no recommendation for or against IVA/LUM combination therapy for individuals with a diagnosis of CF and two copies of the F508del mutation who are aged 0–5 years.

Recommendation 22. The committee suggests IVA/LUM combination therapy for individuals with a diagnosis of CF and two copies of the F508del mutation who are aged 6–11 years with $PPFEV_1$ less than 40% (Conditional recommendation; Very Low certainty in the evidence).

Recommendation 23. The committee suggests IVA/LUM combination therapy for individuals aged 6–11 years with a diagnosis of CF and two copies of the F508del mutation with $PPFEV_1$ 40%–90% (Conditional recommendation; Very Low certainty in the evidence).

Recommendation 24. The committee suggests IVA/LUM combination therapy for individuals aged 6–11 years with a diagnosis of CF and two copies of the F508del mutation with $PPFEV_1$ greater than 90% (Conditional recommendation; Very Low certainty in the evidence).

Recommendation 25. The committee suggests IVA/LUM combination therapy for individuals aged 12–17 years with a diagnosis of CF and two copies of the F508del mutation with $PPFEV_1$ less than 40% (Strong recommendation; Moderate certainty in the evidence).

Recommendation 26. The committee suggests IVA/LUM combination therapy for individuals aged 12–17 years with a diagnosis of CF and two copies of the F508del mutation with $PPFEV_1$ 40%–90% (Strong recommendation; Moderate certainty in the evidence).

Recommendation 27. The committee suggests IVA/LUM combination therapy for individuals with a diagnosis of CF and two copies of the F508del mutation who are aged 12–17 years with $PPFEV_1$ greater than 90% (Conditional recommendation; Low certainty in the evidence).

Recommendation 28. The committee suggests IVA/LUM combination therapy for individuals aged 18 years or older with a diagnosis of CF and two copies of the F508del mutation with $PPFEV_1$ less than 40% (Strong recommendation; Moderate certainty in the evidence).

Recommendation 29. The committee suggests IVA/LUM combination therapy for individuals aged 18 years or older with a diagnosis of CF and two copies of the F508del mutation with $PPFEV_1$ 40%–90% (Strong recommendation; Moderate certainty in the evidence).

Recommendation 30. The committee suggests IVA/LUM combination therapy for individuals aged 18 years or older with a diagnosis of CF and two copies of the F508del mutation with $PPFEV_1$ greater than 90% (Conditional recommendation; Low certainty in the evidence).

Definitions

Determinants of the Quality of Evidence (Confidence in the Estimates of Benefits, Harms, Burden, Costs)

Although the quality of evidence represents a continuum, the GRADE approach results in an assessment of the quality of a body of evidence in one of four grades.

Quality of Evidence Grades

Grade	Definition
High	The committee is very confident that the true effect lies close to that of the estimate of the effect.
Moderate	The committee is moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	The committee's confidence in the effect is limited. The true effect may be substantially different from the estimate of the effect.
Very Low	The committee has very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

Quality of evidence is a continuum; any discrete categorization involves some degree of arbitrariness. Nevertheless, advantages of simplicity, transparency, and vividness outweigh these limitations. Four key factors influence the direction and the strength of a recommendation.

Domains That Contribute to the Strength of a Recommendation

Domain	Comment
Balance between desirable and undesirable outcomes (trade-offs) taking into account: best estimates of the magnitude of effects on desirable and undesirable outcomes importance of outcomes (estimated typical values and preferences)	The larger the differences between the desirable and undesirable consequences, the more likely a strong recommendation is warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely a weak recommendation is warranted.
Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)	The higher the quality of evidence, the more likely a strong recommendation is warranted.
Confidence in values and preferences and their variability	The greater the variability in values and preferences, or uncertainty about typical values and preferences, the more likely a weak recommendation is warranted.
Resource use	The higher the costs of an intervention (the more resources consumed), the less likely a strong recommendation is warranted.

Interpretation of the Strength of Grading of Recommendations, Assessment, Development, and Evaluation Recommendations

Implications	Strong Recommendation	Conditional Recommendation

Implications	Strong Recommendation	Conditional Recommendation
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that clinicians must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals make decisions consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy in most situations.	Policy making will require substantial debate and involvement of various stakeholders.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Cystic fibrosis (CF)

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Medical Genetics

Pediatrics

Pulmonary Medicine

Intended Users

Physicians

Guideline Objective(s)

To develop evidence-based guidelines for cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulator therapy in patients with CF

Target Population

Patients with cystic fibrosis (CF)

Note: For this guideline, the committee defined patients with CF as individuals who met Cystic Fibrosis Foundation (CFF) criteria for diagnosis of CF (i.e., a clinical presentation consistent with CF, a positive CF newborn screening test, or family history of CF) combined with evidence of abnormal cystic fibrosis transmembrane conductance regulator (CFTR) function, as demonstrated by elevated sweat chloride, detection of two CF-causing CFTR mutations, or abnormal nasal potential differences.

Interventions and Practices Considered

Cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulators, including ivacaftor (IVA) and IVA combined with lumacaftor (LUM; IVA/LUM)

Major Outcomes Considered

- Absolute change in percent predicted forced expiratory volume in 1 second ($PPFEV_1$)
- Upper respiratory symptoms
- Lower respiratory symptoms
- Cough
- Pulmonary exacerbations
- Quality of life measured by CF Questionnaire–Revised (CFQ-R)
- Body mass index
- Adverse events, including serious adverse events
- Glycemic control
- Microbiological profile
- Burden of care

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The committee developed clinical questions using the PICO (Patient, Intervention, Comparator, and Outcomes) format. In developing questions, the committee focused on issues of interest and importance to cystic fibrosis (CF) clinicians, patients, and their families. The committee chose not to address clinical situations for which recommendations have already been published (e.g., ivacaftor [IVA] therapy for patients aged 12 years or older with CF who carry at least one copy of the G551D mutation or 2- to 5-year-old patients with CF with gating mutations other than G551D) or if the question was of low priority and unlikely to change practice (e.g., IVA/lumacaftor [LUM] therapy for patients with CF with only one copy of F508del). A systematic review of peer-reviewed literature published from database inception through April 2016 was conducted in Ovid, EMBASE, PubMed, Cochrane Library Scopus, and Google Scholar. They repeated the search in September 2017 and found no relevant new citations.

This search yielded 278 published reports that were examined independently by two reviewers against a set of eligibility criteria. These criteria were defined by the Committee, and they required that included studies be randomized, controlled trials, that the studies directly address one of the four PICO questions, that there was an appropriate comparison group, and that at least one of the outcomes of interest was reported.

Full details of the data review, grading, and evidence-to-decision tables are available in the online supplement (see the "Availability of Companion Documents" field).

Number of Source Documents

The search effort yielded five studies that met eligibility criteria. Several months after these studies were identified, a sixth study was published, and data from that study were added to the meta-analysis. Shortly before this report was completed, a seventh study was published. Data from that study are not included in this report.

See the "Summary of Evidence" sections in the original guideline document for the number of studies included for each question.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Determinants of the Quality of Evidence (Confidence in the Estimates of Benefits, Harms, Burden, Costs)

Although the quality of evidence represents a continuum, the GRADE approach results in an assessment of the quality of a body of evidence in one of four grades.

Quality of Evidence Grades

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Quality of evidence is a continuum; any discrete categorization involves some degree of arbitrariness. Nevertheless, advantages of simplicity, transparency, and vividness outweigh these limitations. Four key factors influence the direction and the strength of a recommendation.

Domains That Contribute to the Strength of a Recommendation

Domain	Comment
Balance between desirable and undesirable outcomes (trade-offs) taking into account: best estimates of the magnitude of effects on desirable and undesirable outcomes importance of outcomes (estimated typical values and preferences)	The larger the differences between the desirable and undesirable consequences, the more likely a strong recommendation is warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely a weak recommendation is warranted.
Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of	The higher the quality of evidence, the more likely a strong recommendation is warranted.

evidence for outcomes)

Domain	Comment
Confidence in values and preferences and their variability	The greater the variability in values and preferences, or uncertainty about typical values and preferences, the more likely a weak recommendation is warranted.
Resource use	The higher the costs of an intervention (the more resources consumed), the less likely a strong recommendation is warranted.

Methods Used to Analyze the Evidence

Meta-Analysis

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction Strategy

The research team used RevMan to input data from studies that were eligible for inclusion in the meta-analysis. A RevMan database was customized in a manner that was consistent with the PICO (Patient, Intervention, Comparator, and Outcomes) questions, including all outcomes as well as the subgroup analyses that were defined based on age and percent predicted forced expiratory volume in 1 second ($PPFEV_1$). Within each outcome, the data were input based on ivacaftor dose, creating two subgroups: 150 mg and 250 mg. PICOs #3 and #4 also involved different doses of lumacaftor and these were input separately. A draft of the RevMan database was piloted using one of the papers that was previously determined to be eligible for inclusion in the meta-analysis. Findings from this pilot test resulted in the need to consult with the Committee on several methodological issues, and the database was revised and finalized following these discussions.

Similar to the review of papers for eligibility in the meta-analysis, a parallel data abstraction procedure was followed in which two abstractors entered data into identical copies of the RevMan database. This procedure yielded two data sets that were exported, merged, and compared to identify discrepancies. These discrepancies were discussed and adjudicated, thereby generating a final RevMan database containing information for use in the meta-analysis.

Following parallel data abstraction and adjudication of discrepancies, the research team examined each eligible paper in relation to the PICO questions and subgroup analyses to determine which PICOs and subgroup analyses could be addressed with meta-analysis. This information was provided to physicians on the Committee with accompanying text that summarized which questions had no outcome data, only one source of outcome data, or two or more sources of outcome data. Members of the Committee indicated that these preliminary observations were consistent with their *a priori* expectations.

Assessment of Methodological Quality

Shortcomings in the design or implementation of clinical research can impact the validity of findings. Studies that were eligible for inclusion in the meta-analysis were therefore assessed for methodological quality with the Cochrane risk of bias tool, a feature of the RevMan software package. This process includes evaluation of a number of elements that can potentially impact the robustness of study data. As described in the Cochrane Handbook, parallel design studies, such as those meeting inclusion criteria for this meta-analysis, can be biased in several ways.

- Selection bias
  - Sequence generation
  - Allocation sequence concealment
- Performance bias
  - Blinding of participants
  - Blinding of personnel

- Detection bias
  - Blinding of outcome assessment
- Attrition bias
  - Incomplete outcome assessment
- Reporting bias
  - Selective outcome reporting
- Other sources of bias

The potential for each type of bias within each included study was evaluated as being "high," "low," or unclear.

Data Synthesis

Meta-analytic techniques are used to obtain overall estimates of treatment effect across a series of studies. In settings where the underlying disease and treatment are common, there will be a large number of studies that can be included in a given meta-analysis. When 25 or more studies are available for analysis, there is sufficient information to provide confidence in any combined estimates, confidence intervals and statistical testing. In this setting, both the between and within-study variability can be estimated and used to calculate an overall treatment effect and appropriate meta-analytic methods can be applied.

There are fewer methods available for meta-analysis when the number of studies is small. In fact, one could argue that an assessment of between-study variability is uninformative when only two or three studies are available for analysis. As this is often the case for rare diseases, there has been some statistical development of techniques that can be used for meta-analyses based on a small number of studies. Given the rarity of CF and the limited number of studies available for this analysis, the data were synthesized using both fixed effects and random effects approaches to meta-analysis, including two current statistical approaches for meta-analysis that correct for the combination of a small number of studies. The underlying assumptions made in the computation of confidence intervals and statistical tests, and the properties of each approach are described below.

For research questions with only two pieces of outcome data, only fixed effects results were reported. For research questions with three or more pieces of outcome data, both random effects and fixed effects (as a means of sensitivity to the random effects) were reported. Categorical data were summarized as relative risks and rate ratios with 95% confidence intervals. Rate ratios were reported for outcomes based on symptom data (i.e., a specified set of events used to derive a composite endpoint). For example, where available in a study, each of the symptoms listed in appropriate column of Table 6 in the systematic review (see the "Availability of Companion Documents" field) were combined into a single event of "lower respiratory symptoms." Continuous data were summarized as mean differences with 95% confidence intervals.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Co-chairs of the committee were selected by the Cystic Fibrosis Foundation (CFF) based on their experience in guideline development and their membership on the CFF Guidelines Committee. The committee for these guidelines was composed of an independent, multidisciplinary group of individuals with expertise and experience in CF care, and included pediatric pulmonologists, adult pulmonologists, a pharmacist, a nurse practitioner, and a respiratory therapist. An adult CF patient and a parent of a child with CF were included in the committee. To assist with the systematic data review and evidence grading, the committee also recruited a medical librarian, methodologist, clinical epidemiologist, and biostatistician.

The committee used the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach to assess the evidence and develop recommendations. GRADE classifies recommendations as strong or conditional (i.e., weak) (see the "Rating Scheme for the Strength of the Recommendations" field). The strength of the recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, quality of evidence, variability in values and preferences, and resources. It is important to note that a conditional recommendation means that although the majority of patients and clinicians will follow the recommendation, there will be some conditions in which the recommendation may not be appropriate given individual circumstances, and the ultimate therapeutic decision will be based on clinical factors specific and unique to that individual patient. Conversely, even a strong recommendation should not be rigidly obeyed, and there may be circumstances under which a clinician or patient would not follow a strong recommendation. Further details on how the committee applied GRADE and the evidence-to-decision tables used to generate recommendations are available in the online supplement (see the "Availability of Companion Documents" field).

Rating Scheme for the Strength of the Recommendations

Interpretation of the Strength of Grading of Recommendations, Assessment, Development, and Evaluation Recommendations

Implications	Strong Recommendation	Conditional Recommendation
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that clinicians must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals make decisions consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy in most situations.	Policy making will require substantial debate and involvement of various stakeholders.

Cost Analysis

One cost-effectiveness analysis for the National Health Service in the United Kingdom was reviewed.

Method of Guideline Validation

Not stated

Description of Method of Guideline Validation

Not applicable

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- In clinical trials, ivacaftor (IVA) therapy resulted in lower sweat chloride (a biomarker of cystic fibrosis [CF] transmembrane conductance regulator [CFTR] function), improved lung function, quality of life, and nutritional indices in patients with CF with the G551D mutation.
- Clinical trials of combination IVA/lumacaftor (LUM) therapy in patients with CF homozygous for F508del demonstrated improved lung function and reduced pulmonary exacerbations.

Potential Harms

Both ivacaftor (IVA) and lumacaftor (LUM) are oral medications that can result in systemic side effects and drug interactions.

Qualifying Statements

Qualifying Statements

The views expressed in this document are those of the authors and do not reflect the official policy of the Department of the Army/Navy/Air Force, Department of Defense, or the U.S. Government.

Use of This Guideline

This guideline is not meant to establish a standard of care. Rather, it represents an effort to summarize evidence and provide sensible clinical recommendations based on that evidence. Clinicians, patients, third-party payers, other stakeholders, and the courts should never view these recommendations as dictates. No guideline or specific recommendations can take into account all of the unique clinical circumstances leading to therapy decisions for individual patients. Therefore, no one charged with evaluating clinicians' actions should attempt to rigidly apply the recommendations from this guideline in a global fashion. This guideline is not intended to be a comprehensive review of the treatment of cystic fibrosis (CF), but rather to provide evidence-based recommendations for use of cystic fibrosis transmembrane conductance regulator (CFTR) modulators in different populations of patients with CF. Clinicians, patients with CF, and parents of patients with CF will be able to use these recommendations when considering CFTR modulator therapy.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Ren CL, Morgan RL, Oermann C, Resnick HE, Brady C, Campbell A, DeNagel R, Guill M, Hoag J, Lipton A, Newton T, Peters S, Willey-Courand DB, Naureckas ET. Cystic Fibrosis Foundation pulmonary guidelines. Use of cystic fibrosis transmembrane conductance regulator modulator therapy in patients with cystic fibrosis. Ann Am Thorac Soc. 2018 Mar;15(3):271-80. [44 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2018 Mar

Guideline Developer(s)

Cystic Fibrosis Foundation - Disease Specific Society

Source(s) of Funding

The Cystic Fibrosis Foundation provided funding for face-to-face meetings, telephone conference calls, the methodologist, the biostatistician, and the clinical epidemiologist.

Guideline Committee

Cystic Fibrosis Foundation Guidelines Committee

Composition of Group That Authored the Guideline

Committee Members: Clement L. Ren, Indiana University School of Medicine, Indianapolis, Indiana; Rebecca L. Morgan, McMaster University Faculty of Health Sciences, Hamilton, Ontario, Canada;

Christopher Oermann, Children's Mercy–Kansas City, Kansas City, Missouri; Helaine E. Resnick, Resnick, Chodorow, and Associates, Silver Spring, Maryland; Cynthia Brady, Children's Hospitals and Clinics of Minnesota, Saint Paul, Minnesota; Annette Campbell, Kansas City University of Medicine and Biosciences, Kansas City, Missouri; Richard DeNagel, Patient Community Advisor, New York, New York; Margaret Guill, Dartmouth College Geisel School of Medicine, Hanover, New Hampshire; Jeffrey Hoag, Drexel University College of Medicine, Philadelphia, Pennsylvania; Andrew Lipton, Walter Reed National Military Medical Center, Bethesda, Maryland; Thomas Newton, Miller Children's and Women's Hospital Long Beach, Long Beach, California; Stacy Peters, South Dakota State University, College of Pharmacy, Brookings, South Dakota; Donna Beth Willey-Courand, University of Texas Health Science Center at San Antonio, San Antonio, Texas; and Edward T. Naureckas, University of Chicago, Chicago, Illinois

Financial Disclosures/Conflicts of Interest

When choosing committee members for these guidelines, all potential committee members were asked to complete a conflict of interest (COI) questionnaire regarding both fiduciary and financial relationships with pharmaceutical companies involved in the production of clinically available cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulators. The COI questionnaires were examined by a neutral and unbiased member of the Cystic Fibrosis Foundation (CFF) Guidelines Steering Committee as well as the CFF Director of Medical Compliance. Any potential committee member who disclosed such a relationship was not invited to participate on the committee, and several members of the CFF Guidelines Committee were excluded because of potential conflicts of interest.

Due to the CFF's potential COI in the creation of these guidelines, no CFF staff member participated in writing or discussion of the recommendations, and the CFF neither endorsed nor declined to endorse these recommendations. The only CFF staff present for the discussion of these recommendations were the Practice Guidelines Specialist and the Director of Medical Compliance, and neither of them participated in the creation of questions or the development of any recommendations. The CFF's role in the development of these guidelines was limited to funding for face-to-face meetings, telephone conference calls, the methodologist, the biostatistician, and the clinical epidemiologist. The medical librarian was recruited from Indiana University, which did not charge any fees for her effort.

Disclosures are available from the Annals of the American Thoracic Society Web site .

Guideline Endorser(s)

American Thoracic Society - Medical Specialty Society

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Annals of the American Thoracic Society Web site .

Availability of Companion Documents

The following are available:

Ren CL, Morgan RL, Oermann C, Resnick HE, Brady C, Campbell A, DeNagel R, Guill M, Hoag J, Lipton

A, Newton T, Peters S, Willey-Courand DB, Naureckas ET. Cystic Fibrosis Foundation pulmonary guidelines. Use of CFTR modulator therapy in patients with cystic fibrosis. Online data supplement. 2018 Mar. 454 p. Available from the Annals of the American Thoracic Society Web site .

International Committee of Medical Journal Editors (ICMJE) form for disclosure of potential conflicts of interest. Philadelphia (PA): International Committee of Medical Journal Editors (ICMJE); 44 p. Available from the Annals of the American Thoracic Society Web site .

Resnick HE, Kervin TA, Norris T, Eichorn S, Weissfeld L. CFTR modulator treatment among people with cystic fibrosis and non-G551D CFTR mutations: a systematic review of the evidence. 2016 Nov 9. 189 p. Available on request from the Cystic Fibrosis Foundation.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on May 8, 2018. The information was verified by the guideline developer on May 30, 2018.

This NEATS assessment was completed by ECRI Institute on May 1, 2018. The information was verified by the guideline developer on May 30, 2018.

Copyright Statement

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